PROGESTERONE CHALLENGE TEST IN SCREENING ASYMPTOMATIC POSTMENOPAUSAL WOMEN FOR CANCER BODY UTERUS

THESIS

FOR

MASTER OF SURGERY

(OBSTETRICS & GYNAECOLOGY)

BUNDELKHAND UNIVERSITY
JHANSI

1997

SUJIT KUMAR PRASAD

C E R T I F I C A T E

This is to certify that the work entitled "PROGESTERONE CHALLENGE TEST IN SCREENING ASYMPTOMATIC POSTMENOPAUSAL WOMEN FOR CANCER BODY UTERUS", which is being submitted as a thesis for M.S.(Obstetrics and Gynaecology) Examination, 1998, Bundelkhand University, has been carried out by Dr. Sujit Kumar Prasad in the Department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the department as per university regulations.

Dated : 16/1/98

(Swadesh Sharma)
M.S., FICOG
Professor and Head,
Department of Obstetrics &
Gynaecology,
M.L.B. Medical College,
JHANSI.

C E R T I F I C A T E

This is to certify that the work entitled "PROGESTERONE CHALLENGE TEST IN SCREENING ASYMPTOMATIC POSTMENOPAUSAL WOMEN FOR CANCER BODY UTERUS", which is being submitted as a thesis for M.S.(Obstetrics and Gynaecology) Examination, 1998, Bundelkhand University, has been carried out by Dr. Sujit Kumar Prasad under my direct supervision and guidance. The techniques embodied in this thesis were undertaken by the candidate himself and the observations recorded were checked and verified by me from time to time.

Dated : 16.1.98

(Mridula Kapoor)
M.S.,
Associate Professor,
Department of Obstetrics &
Gynaecology,
M.L.B. Medical College,
JHANSI.

(GUIDE)

C E R T I F I C A T E

This is to certify that the work entitled "PROGESTERONE CHALLENGE TEST IN SCREENING ASYMPTOMATIC POSTMENOPAUSAL WOMEN FOR CANCER BODY UTERUS", which is being submitted as a thesis for M.S.(Obstetrics and Gynaecology) Examination, 1998, Bundelkhand University, has been carried out by Dr. Sujit Kumar Prasad under my direct supervision and guidance. The techniques embodied in this thesis have been undertaken by the candidate himself and observations recorded were checked and verified by me from time to time.

Dated : 13/1/98

(Sunita Arora)
M.S.,
Associate Professor,
Department of Obstetrics &
Gynaecology,
M.L.B. Medical College,
Jhansi.

(CO-GUIDE)

C E R T I F I C A T E

This is to certify that the work entitled "PROGESTERONE CHALLENGE TEST IN SCREENING ASYMPTOMATIC POSTMENOPAUSAL WOMEN FOR CANCER BODY UTERUS", which is being submitted as a thesis for M.S.(Obstetrics and Gynaecology(Examination, 1998, Bundelkhand University, has been carried out by Dr. Sujit Kumar Prasad under my direct supervision and guidance. The techniques embodied in this thesis have been undertaken by the candidate himself and observations recorded were checked and verified by me from time to time.

Dated : 16/1/98

(Usha Agarwal)
M.S.,
Associate Professor,
Department of Obstetrics &
Gynaecology,
M.L.B. Medical College,
Jhansi.

(CO-GUIDE)

C E R T I F I C A T E

This is to certify that the work entitled "PROGESTERONE CHALLENGE TEST IN SCREENING ASYMPTOMATIC POSTMENOPAUSAL WOMEN FOR CANCER BODY UTERUS", which is being submitted as a thesis for M.S.(Obstetrics and Gynaecology) Examination, 1998, Bundelkhand University, has been carried out by Dr. Sujit Kumar Prasad under my direct supervision and guidance. The techniques embodied in this thesis have been undertaken by the candidate himself and observations recorded were checked and verified by me from time to time.

Dated : 16/1/98

(Sanjaya Sharma)
M.D.,
Assistant Professor,
Department of Obstetrics &
Gynaecology,
M.L.B. Medical College,
Jhansi.

(CO-GUIDE)

A C K N O W L E D G E M E N T

I am indebted to my esteemed and learned teacher Dr. Swadesh Sharma, M.S. Professor and Head, Department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi for whom my reverence has always been at its zenith. Her sweet nature and sympathetic attitude has contributed a lot towards the success of this work.

It is with due regards that I pay mt gratitude to my respected and learned teacher and guide Dr.Mridula Kapoor, M.S., Associate Professor, Department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi for her valuable advice and suggestions which played an important role in successful completion of the present work.

I am greatly indebted to my co-guide Dr. Sunita Aroa, M.S., Associate Professor, Department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi for her timely advice and help.

I am thankful to Dr. Usha Agarwal, M.S. Associate Professor, Department of Obstetrics & Gynaecology, for her constant supervision and timely advice for the present work.

I am greatly indebted to my co-guide Dr. Sanjaya Sharma, M.D., Assistant Professor, Department of Obst. & Gynaecology, who has spared invaluable time in correction and guided me in each and every step, which lead to completion of this work. Without her support it would have not been possible to accomplish the project for me.

I sincerely thank to Dr. V.K. Sharma, M.D., Head, Department of Pathology for his kind advice and suggestions.

I also thank my seniors and colleagues of this department for their help which lead to completion of this work.

I bow in reverence to my lady subjects who have formed the material for the present study. Nothing can replace them.

I thank Shri Phool Chandra Sachan for his help in typing the manuscript of this thesis.

Lastly I pay my regards to my parents who have supported me morally and have helped me in each and every step of life.

Sujit Kumar Prasad.

Dated : 16/1/98

(Sujit Kumar Prasad)

I N T R O D U C T I O N

INTRODUCTION

Endometrial carcinoma is the second most common cancer of genital tract occurring in females in India. It has been assumed that overall 2-3% of women develope endometrial cancer in their life time.

In India for each cancer of endometrium there are 25% cases of cancer cervix. However, the incidence of carcinoma endometrium is increasing due to :

- Greater life expectancy.
- Greater availability of medical care and
- Increased use of oestrogen.

Various methods are available like cervico vaginal smear, vaginal pool cytology, endometrial lavage cytology, and aspiration cytology, detecting 40-70%, 48%, 63% and 90% of cases respectively. However, these methods are associated with patient discomfort, relatively low yield and lack of cost effectiveness. Considering above factors, it has become of immense importance that the cancer should be detected in earlier stages, as soon as possible.

Various premalignant conditions of the endometrium like endometrial hyperplasia is more likely to develope after prolonged period of anovulation and unopposed oestrogen stimulation.

Natural history of this disease as suggested by Hofmeister (1974) is graphically designated as :

Endometrial polyp being one of the preconditions ----- ,
---Adenomatous hyperplasia <----- Cystic hyperplasia<----
--->Anaplasia ---> Carcinoma in situ -----> Carcinoma.

Hyperplasia can be of simple hyperplasia, complex hyperplasia, and atypical hyperplasia depending on the grandular architecture and cytologic atypia.

The risk of endometrial hyperplasia progressing to carcinoma is related to the presence and severity of cytologic atypia. According to Kurmar et al (1987) progression to carcinoma occurred in 1% patients with simple hyperplasia, 3% in patients with complex hyperplasia and 29% in patients with atypical complex hyperplasia.

In 25% of cases there may be evidence of endometrial hyperplasia preceding the development of endometrial carcinoma. Progression to endometrial carcinoma depends on the age of patient, stage of the disease, type of growth whether associated with diabetes, hypertension, in the line of treatment adopted when only endometrium is involved almost 100% salvage can be achieved with Pan hysterectomy. With superficial myometrial infiltration the 5 years survival in 75-80% . However, the salvage rate drops to 50% if there is extensive myometrial or cervical involvement. With extra-uterine extension of the disease, the survival is less than 20% (Mc Lenon, 1976).

Routine papanicolaou testing is inadequate and endometrial cytology assessment is too insensitive and non-specific to be useful in screening for endometrial cancer even in high risk population.

Gambrell et al (1991) advocated the use of progesterone challenge test in an attempt to remove the draw back

associated with other methods available till now. Various authors (Hanne et al, 1983; Toppozeda et al, 1988) have also tried progesterone challenge test as a screening test for endometrial carcinoma.

After administration of progesterone challenge test to asymptomatic post menopausal women, the presence or absence of withdrawal bleeding may add in detecting premalignant lesion of endometrium or endometrial carcinoma, and therefore could be used as screening procedure in post menopausal women at risk for developing endometrial carcinoma.

Progesterone challenge test will reveal whether the endometrium has been primed by oestrogen but it will not identify about endometrial pathology.

In progesterone challenge test (PCT), there is progesterone induced withdrawal bleeding. A positive progesterone challenge test indicates :

1. The presence of uterus with endometrium capable of a normal response to ovarian steroids (endometrium is primed by oestrogen).
2. The presence of some endogenous oestrogenic activity which in turn indicates -
   a. The presence of minimal ovarian activity.
   b. The presence of gonadotrophic stimulation, sufficient for evoking follicular maturation.
   c. The presence of hypothalamic LHRH activity sufficient for basic pituitary stimulation.

Gambrell et al (1980) used progesterone challenge test to identify post menopausal women at risk for adenocarcinoma of endometrium. This included 100 asymptomatic postmenopausal women in their study. Progesterone and challenge test and endometrial biopsy both were done in all cases. 86 women exhibited no withdrawal bleeding. In all these cases the histology was normal, 14 women exhibited withdrawal bleeding. 9 of whom had unsuspected adenomatous hyperplasia and the other 5 had atypical endometrium.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The post menopausal endometrium has been classified by Novak and Richardson (1941) as follows :

I. ATROPHIC ENDOMETRIUM : Endometrium is thin, the surface and glandular epithelium is either of normal or less fibrotic and the glands sparse and most infrequently cystic. This is mot commonly found.

II. PROLIFERATIVE ENDOMETRIUM : Similar to that found in follicular phase of menstrual cycle during reproductive period.

III. ACTIVE HYPERPLASIA: Characterised by Swiss-Cheese pattern, an intact epithelium with often dark staining nuclei and abundant compact stroma.

IV. RETROGRESSIVE HYPERPLASIA : The Swiss-Cheese gland pattern is perfectly marked here. Epithelium is often low and atrophic and the stroma is obviously fibrotic and inactive. The fibrotic appearance of the stroma appears to be a more reliable indicator of hormonal inactivity than does the epithelium which may remain tall and inactive for many years; after the menopause even when the stroma is very fibrotic.

Endometrial cancer is a disease that occurs primarily in postmenopausal women and is increasingly virulent with advancing age. The role of estrogen in the development of most endometrial cancer has been established

clearly, any factor that increases exposure to unopposed oestrogen increases the risk of endometrial cancer (Novak's Gynaecology, 12th edition).

ENDOCRINOLOGICAL CHANGES IN THE POST MENOPAUSAL WOMEN

With approach of menopause, the oestradial levels in the blood may be low (50-100 ng/l) as compared to 150 ng/l in younger women. The FSH levels may be elevated to twice the level seen during the follicular phase of younger women. There is no significant alteration in the LH levels. After menopause, due to very low levels of oestradial (10-15 ng/l) caused by ovarian follicular failure, the FSH levels get markedly elevated to 10-20 times higher than in younger women with LH about three times higher. The circulating oestrogen in postmenopausal women is mainly oestrogen rather than oestradiol unlike in the young. Most of the oestrogens are now derived by the peripheral conversion of androtenodione to oestrone. The adrenal cortex (which produces the androtenodione) and the ovarian cortical stroma are the main sources of steroids. As the ovary is responsible for 50% of testosterone production, the plasma testostwrone falls only slightly after menopause from about 300 ng/l to 230 ng/l. This fall may be more marked in those who had oophorectomy. The hormonal levels may vary depending upon the time of the day, the number of years following menopause and type of menopause whether spontaneous or surgically induced.

Endometrial hyperplasia rapresents a spectrum of mrophologic and biologic alteration of the endometrial

glands and stroma, ranging from an exaggerated physiologic state to carcinoma in situ. Endometrial hyperplasia are important clinically because they may cause abnormal uterine bleeding, may be associated with estrogen producing ovarian tumour, may result from hormonal therapy and may precede or occur simultaneously with endometrial cancer. Endometrial hyperplasia has been classified by the International Society of Gynaecological Pathologists into the simple hyperplasia, complex hyperplasia and atypical hyperplasia.

Simple hyperplasia is characterised by dilated or cystic glands with round or slightly irregular shapes, an increased glandular to stromal ratio without glandular crowding and no cytologic atypia. Complex hyperplasia has architecturally complex (budding and infolding) crowded glands with less intervening stroma without atypia.

Atypical hyperplasia refers to cytologic atypia and can be categorised as simple or complex, depending on the corresponding glandular architecture. Criteria for cytologic atypia include large nuclei of variable size and shape that have lost polarity, increased nuclear to cytoplastic ratio, prominant nucleoli and irregularly clumped chromatic with parachromatic clearing.

The risk of endometrial hyperplasia progressing to carcinoma is related to the presence and severity of cytologic atypia. According to Kurmar et al (1987) progression to carcinoma occurred in 1% of patients with simple hyperplasia, 3% with complex hyperplasia, 8% of patients with

atypical simple hyperplasia and 29% of patients with atypical complex hyperplasia. Most of the hyperplasia seems to remain stable (18%) or regress (7.4%). The premalignant potential of hyperplasia is influenced by age, underlying ovarian disease, endocrinopathy, obesity and exogenous hormone exposure. In patients with atypical hyperplasia detected during endometrial biopsy or in a curettage specimen, approximately 25% will have an associated usually well differentiated endometrial carcinoma, if hysterectomy is performed.

Cullen (1900) described that endometrial carcinoma began with anovulatory cycles :

Anovulatory bleeding
|
Cystic glandular hyperplasia
|
Adenomatous hyperplasia
|
Adenocarcinoma in situ
|
Invasive adenocarcinoma

Backer (1904) first noted that there is an association between endometrial hyperplasia and subsequent endometrial carcinoma.

Gusberge (1947) introduced the designation adenomatous hyperplasia to include the entire spectrum of precancerous architectural and cytological abnormalities of endometrium. It has well been documented that this hyperplasia may be precursor to adenocarcinoma of endometrium in some women. Gusberg (1976) showed that among patients with adenomatous hyperplasia 18.5% with short (5 yrs)

follow-up and 30% after 10 years will develop endometrial cancer.

Precancerous lesions of endometrium are -

1. Cystic hyperplasia.
2. Atypical proliferative hyperplasia, cellular and architectural.
3. Atypical secretary hyperplasia.
4. Carcinoma in situ.
5. Polyps with forgoing changes.

Stromal invasion must be present for diagnosing invasive cancer (Kurmar and Morris, 1982).

The new classification formulated by W.H.O. Committee on endometrial tumours breaks down endometrial hyperplasia into 4 stages.

1. Simple hyperplasia without atypia (SH).
2. Simple hyperplasia with atypia (SAH).
3. Complex hyperplasia without atypia (CH).
4. Complex hyperplasia with atypia (CAH).

According to Norris et al (1986), non atypical hyperplasia, glandular or epithelial occur in women with abnormal endocrine milieu. The potential for progression to carcinoma is minimal in these groups (2%). Of these who have atypical hyperplasia it was shown in one study that 23% progressed to carcinoma. It was, therefore, presumed thatncytologic atypia signifies a high risk for carcinoma and determines the basis for therapy.

The term atypia refers to cellular atypia and the term complexity refers to severe architectural abnormality close to that seen in cases of well differentiated adenocarcinoma.

Simple hyperplasia : It induces cystic hyperplasia and mild and moderate degrees of architectural abnormality. It is not significantly precancerous.

Simple hyperplasia with atypia deserves further investigation as there has not been enough follow up information. When complex hyperplasia with atypia is diagnosed in a biopsy specimen, a well differentiated adenocarcinoma is discovered in the hysterectomy specimen in 15 to 20% of the cases. Or the lesion will eventually be followed by carcinoma in approximately 30% of the patients (Tavassali F and Krause FT, 1978 and Kurman RI and Norris H., 1982).

ATYPICAL HYPERPLASIA Vs WELL DIFFERENTIATED ADENOCARCINOMA

Handerickson et al (1983) and Kurmar and Norris (1982) had laid down the criteria "The first group undefined various architectural and cytologic abnormalities some of which may be absent in individual cases, leaving the final decision to the overall evaluation of the lesion. Both pronounced architectural atypia and at least moderate cytologic abnormality are required.

The second group emphasized architecture qualities stromal and quantitative features. Primary criteria for adenocarcinoma the presence or absence of stromal invasion, which is defined arbitrarily by the presence of at least one of the following features :

1. Desmoplastic stromal response in the vicinity of infiltrating glands.
2. Confluent or cribiform glandular pattern.
3. Extensive papillary pattern and
4. Replacement of stroma by squamous epithelium.

In a retrospective study Hartig and Sommens (1949) observed 32 cases of complex hyperplasia and atypical hyperplasia was found to antecedate carcinoma by 1.5 years and in other hyperplasia by 6-7 years. Cystic hyperplasia is only weekly precancerous was presented by Mebride (1959) who followed for 24 years and found that carcinoma develope only in 29% of cases. Normal findings on chromosomal and DNA studies are also consistent with a low malignant potential. Gustiberg and Kaplan (1963) recorded follow up on 191 patients. 80% of the patients were more than 40 years and 12% of patients where hysterectomy was not done, developed carcinoma endometrium (68/101) were followed for one year.

Chamberlain and Taylor (1970) investigated 97 patients of adenomatous atypical hyperplasia. 14% developed carcinoma in 1-14 years.

Wentz (1974) reported follow up of 115 cases for 2-3 years. 27% adenomatous hyperplasia, 82% atypical hyperplasia and all cases of carcinoma in situ had developed carcinoma.

Sherman and Brown (1979) followed for 2-18 years, 216 untreated patients of 50 years of age with complex hyperplasia and 39% of cases had carcinoma later on (22% adenomatous, 57% atypical adenomatous, 59% carcinoma in situ). Regression of process of endometrial hyperplasia is certainly more frequent than progression to neoplasia. The risk of developing adenocarcinoma increases with the spectrum of morphology being lowest for cystic hyperplasia, greater for adenomatous hyperplasia and greatest for atypical hyperplasia.

Screening Technique used for detection OF endometrial carcinoma

Carcinoma of uterus is one of the common malignancies of female genital tract. Early diagnosis of the disease can lower the morbidity and mortality associated with it. Attempt to identify premalignant and silent cancer of uterus have been made. A single diagnostic procedure has not been uniformly successful. It would appear that multiple techniques using both cytologic and histologic material would increase the possibility of achieving the goal for early diagnosis of uterus cancer.

It was Slauter (1902) who used first endometrial biopsy as a diagnostic procedure for endometrial carcinoma in both symptomatic and asymptomatic post menopausal women.

Papanicalou and Traut (1943) advocated vaginal pool smear technique for early detection of endometrial carcinoma. This method is now abandoned in favour of direct endometrial sampling. The vaginal pool smear techniques was time consuming and was less efficient than the direct endometrial sampling in the detection of endometrial lesion. For screening purpose, the vaginal pool smear should be obtained on every woman who crosses the age of 50, as it may contribute significantly to the diagnosis of endometrial cancer in early stages.

Herling and Sammers (1949) indicated that adenomatous hyperplasia preceded carcinoma. Palmer (1950) diagnosed endometrial carcinoma by endometrial biopsy. He reported about 92% accuracy rate in his study.

Hechte (1954) used aspiration cytology to diagnose endometrial carcinoma. He included 901 patients ranging in from 20 to 71 years, the average being 51 years. 71 cases were post menopausal with bleeding per vaginum. Out of which 38 patients were diagnosed as cases of endometrial carcinoma.

Way (1956) had drawn attention to an interesting fact that carcinoma body uterus was associated with late menopause, obesity, hypertension, presence of fibroid, nulliparity and diabetes in many patients.

Sippe (1962) in his study of 282 cases noted that the endometrial hyperplasia was a common uterine disorder occurring particularly during climatric. He found that 80% of cases were in the age group of about 40-50 years. On histopathological examination, there were large blood

sinuses with inconspicuous wall which were commonly found in the superficial endometrium and rupture of these sinuses had been responsible for uterine haemorrhage.

Devi (1964) stated that endometrial cancer was usually a disease associated with post menopausal women. The peak incidence of endometrial carcinoma in his series was towards the end of the 6th decade of life. 10-15 years after menopause most of the cases diagnosed were in the 50 to 60 years of age group. The disease was rare before 20 years and after 90 years of age.

Coleman (1965) used vaginal cytology to detect uterine malignancy in early stage. He selected 285 patients for study and found atypical cells in 185 patients, 78 patients showed negative report, 22 patients showed unsatisfactory findings.

Robert (1965) pointed out that there was a strong association between persistent unopposed oestrogen action in the absence of ovulation with increased risk of endometrial cancer. Two pathways seemed to be involved in this process.

In first excessive or unopposed 17 extradiol was secreted either continuously over long period of time or in fluctuation. So that the endometrium was stimulated from the stage of normal proliferation to hyperplasia, atypical hyperplasia and eventually to carcinoma in some cases. This would appear to be a major mechanism in those postmenopausal cases in whom progression through atypical hyperplasia to carcinoma takes place. The other pathway involved was the production of oestrone by extraglandular

conversion of androstemedione. This would appear to be the most common root in postmenopausal women. The oestrone may have sufficient estrogenic activity to cause proliferative changes in the endometrium but it provides facultative support in development of cancer. However, when the production of estrone is increased by any mechanism, the chances of developing endometrial cancer are greatly increased.

Wynder (1966) concluded that obesity was a major risk factor most commonly associated with endometrial carcinoma. In women who were 21-50 pounds over weight omcodemce of endometrial carcinoma has increased three fold. In women 50 pounds or more over the ideal weight the risk was 5 times greater than women of normal weight.

In Peterson's series (1968), a total of 81% patients with endometrial carcinoma weighed over 150 pounds while 63% of the group weighed over 180 pounds and 7% over 230 pounds.

Gravlee (1969) advocated jet washing technique for establishing early diagnosis of endometrial carcinoma particularly in asymptomatic patients. 181 patients were sampled with jet washer. 135 patients out of 181 showed atypical cytology, 10 of which were found to have endometrial carcinoma. On curetting failure rate was 21%.

Bonham (1973) reported from his own clinic that the peak occurrence of this disease was between the age of 50 and 60 years. When diagnosis was made before the menopause, as occur in 20 to 25% of cases. The clinical outcome was definitely more favourable. In general the early onset of this disease was more frequently associated with femini-

zing ovarian tumours and polycystic ovarian disease.

Gushberg (1973) reported that endometrial carcinoma tended to occur one decade later in life than cervical cancer. This occurred because endometrial carcinoma, seem to be some combination of hormonal disturbance that occur after menopause or whenever oestrogen activity in excess or is unopposed by activity of progesterone.

Kelly et al (1973) advocated the use of endometrial biopsy as an outdoor procedure in order to obtain adequate endometrial tissue for diagnostic study. Many other authors have also advocated the use of endometrial biopsy as a routine outdoor procedure and in their hands it has become a good screening technique.

Knoll (1974) evaluated the utility of vaccum aspiration method in diagnosis of asymptomatic patients. There were 122 patients evaluated by vaccum aspiration of endometrial cavity. 72 out of 122 patients had abnormal cytology. 10 out of 72 patients were diagnosed as having endometrial carcinoma also proved by endometrial biopsy.

Hofmeister (1974) for the first time used endometrial biopsy as a routine office procedure in more than 20,000 postmenopausal women. He noted that in 17% cases, endometrial carcinoma was diagnosed in asymptomatic women.

Kaplan and Cole (1974) suggested that diabetes mellitus may be associated with increased risk of endometrial carcinoma. He reported that the risk with abnormal glucose tolerance is 2-4 times higher than when it is absent.

Smith (1975) showed positive association between endometrial carcinoma and hypertension. The triad of diabetes mellitus, obesity and hypertension occurs most commonly in patients of the age group of 60-70 years. This triad had been dubbed as "The corpus cancer syndrome".

Out patients diagnostic technique is comparable to the papanicoloau. Smear for carcinoma of cervix, to permit an early recognition of endometrial cancer. Five different techniques of sampling of the endometrial cavity were saline irrigation with antrum cannula, endometrial brush sampling, high vaccum aspirator, Gravlee jet washer and endometrial biopsy. Out of these five methods, endometrial biopsy permitted accurate diagnosis (David and Anderson, 1976).

Creasman (1976) studied 640 patients selected from out door and indoor. The age varying from 40 to 70 years. Endometrial cytology was done by Vabra technique. He found that 80% adenocarcinoma and adenomatous hyperplasia could be diagnosed by this technique. He also evaluated the utility of combination of several techniques when brush and endometrial biopsy were combined, 19 out of 21 patients could be diagnosed as suffering from endometrial carcinoma.

David (1976) evaluated the different screening procedures and proposed saline irrigation as a simple outdoor screening procedure which could be utilized to diagnose endometrial carcinoma in early stage. Out of 125 patients who underwent saline irrigation of endometrium cavity, 64 patients were having endometrial hyperplasia. Failure rate of this procedure was 22%.

Second technique used was brush technique. In this group 191 patients were subjected to endometrial brush sampling. There were 11 patients with endometrial adenocarcinoma proved by endometrial curettings. 118 cases were having atypical cytological findings. However, cytology was unsatisfactory in 62 patients. Failure rate of this method was very high about 36%.

Peter (1976) noted that all endometrial tumour had low progesterone binding capacity. By means of dextron coated charcoal assay, the capacity of various endometrial cytol preparation for specific binding of progesterone was determined. Two out of 7 grade I, 3 out of 8 grade II and 2 out of 3 grade III endometrial carcinoma showed low binding capacity. These data suggested a progressive loss of specific progesterone binding capacity from normal to hyperplastic endometrium and from well differentiated to anaplastic form of adenocarcinoma. The author calculated that the use of progesterone binding capacity may help in diagnosing the asymptomatic and symptomatic patients at risk for endometrial carcinoma.

Cohen (1977) stated that an accurate endometrial cytology screening test would be of particular value in the continuing surveillance of patients with abnormal uterine bleeding in the follow up evaluation of patients with documented atypical endometrium and perhaps as a part of the periodic examination of all menopausal and post menopausal patients.

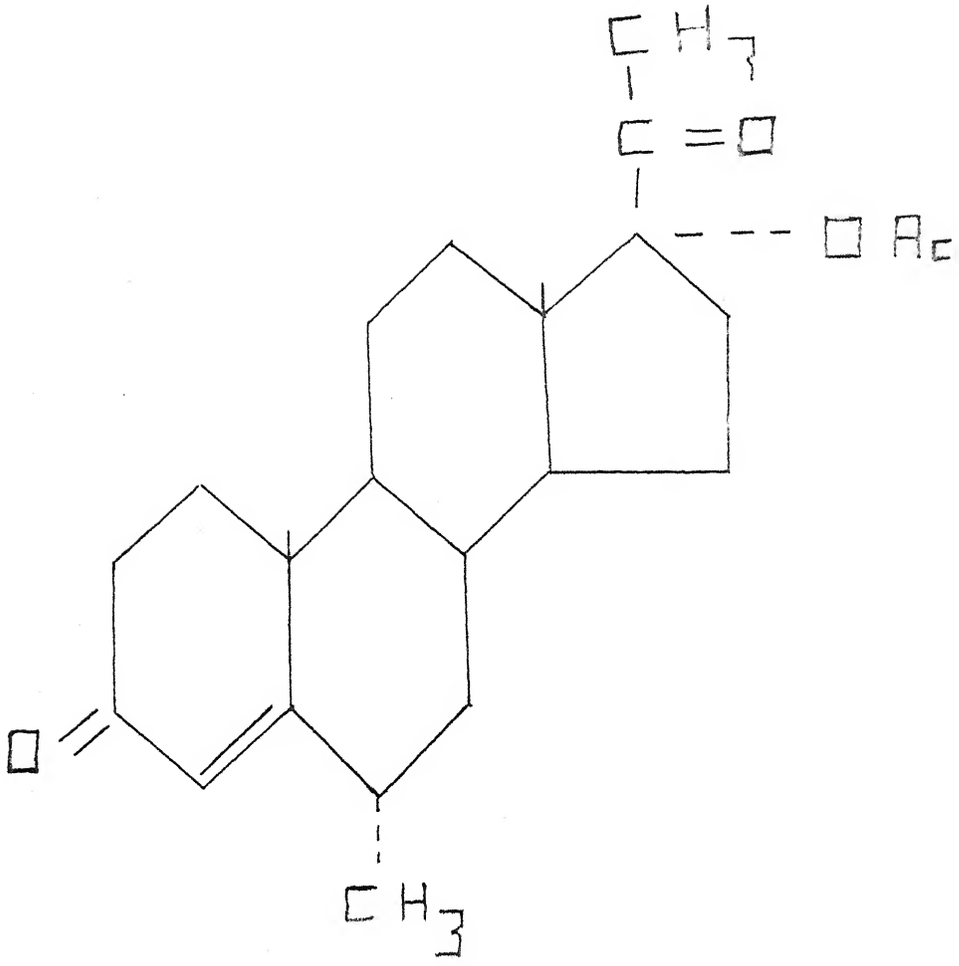
Welch and Scully (1977) pointed out that stimulation of endometrium by exogenous or endogenous oestrogen resulted in hyperplasia or carcinoma body uterus or to cause abnormal vaginal bleeding. In his study he noted that 25% of cases having hyperplastic endometrium, converted into endometrial carcinoma in five years or more time.

The technique so far discussed for diagnosis of endometrial carcinoma had all been invasive in nature, procedures being relatively unsafe, time consuminf, costly and success rate achieved by them have been rather low.

Gambrell et al (1980) gave an illustrated view regarding the quality of outdoor screening procedures for diagnosis of endometrial carcinoma. They stated that the method should be acceptable to the patients, be painless, inexpensive and reliable in the hands of all those doing the pelvic examination. They recognised the need for a technique that would permit early diagnosis of endometrial carcinoma.

Progesterone counter the effect of oestrogen and causes sloughing of endometrium and withdrawal bleeding induced by progesterone intake in an indication of presence of oestrogen in sufficient quantity to proliferative endometrium.

In post menopausal women suspected for endometrial carcinoma administration of progesterone will cause withdrawal bleeding to occur after the progesterone is stopped based on this principle is the progesterone challenge test developed by Gambrell and co-authors at Warfoy Hall, U.S.A.F.



MEDROXYPROGESTERONE ACETATE
STRUCTURE

Medical Centre to detect endometrial carcinoma.

Currently, Hanne et al (1983) noted the use of progesterone challenge test in asymptomatic postmenopausal women. According to them, the presence or absence of withdrawal bleeding aid in detecting premalignant lesion of endometrium. In 1981 they selected 30 women for the study. Both progesterone challenge test and endometrial biopsy were done in all the cases. 25 women exhibited no withdrawal bleeding and had no pathological lesion (Histology was normal). Five women exhibited withdrawal bleeding. Three out of five positive cases had unsuspected hyperplasia, one of which was atypical and two had atypical endometrium. In 1983, they selected 10 post menopausal women with biopsy proved adenomatous hyperplasia who had presented with bleeding symptoms for progesterone challenge test. No specific selection criteria were used. 9 of these 10 exhibited withdrawal bleeding. The purpose of this study was only to establish a false negative rate for progesterone challenge test in known cases of hyperplastic endometrium.

STRUCTURE OF MEDROXY PROGESTERONE ACETATE

Pharmacology of Medroxy Progesterone Acetate

It is a derivative of 17, 6 methyl medroxy progesterone acetate.

It is a highly active progestational agent, white to off white colourless crystalline powder partially soluble in water.

Physiological Activity

Medroxy Progesterone acetate shows exceptionally high progestational activity when administered in tablet form by mouth or in form of Depo provera by intramuscular injection. Comparative studies in immature female rabbit indicate that MPA in 24 to 28 times as potent as other progestational agents.

Clinical Study

The effectiveness of MPA producing secretary changes in endometrium and other progestational effects have been studied in surgically castrated patients with functional uterine bleeding and dysmenorrhoea.

It is used for detection of premalignant condition of endometrium. It causes withdrawal bleeding when administered in patients at risk for endometrial carcinoma or premalignant lesion.

Adverse Effects

It is well tolerated both locally and systemically. There were no estrogenic or androgenic effect after administration. Menstrual irregularity is the main adverse effect when used over prolonged period.

Preparation

MPA is marketed by name of :

1. Devicy - 2.5 mg/5mg/10 mg tabs.
2. Inodin - 2.5 and 10 mg tabs.

MATERIAL AND METHODS

MATERIAL AND METHODS

The present study was conducted in the Departments of Obstetrics & Gynaecology, Pathology and Bacteriology, M.L.B. Medical College, Hospital, Jhansi.

SELECTION OF CASES

Cases were selected from out patients department and wards of Obstetrics & Gynaecology. 100 postmenopausal patients were selected for study. Patients selected had their last menstrual period at least 6 months back. Cases were divided into two groups :

Asymptomatic group

This group comprised of 50 postmenopausal women with no history of bleeding per vagina.

Symptomatic group

This group also comprised of 50 postmenopausal women with history of bleeding per vagina.

CLINICAL HISTORY

Detailed history of each patient was taken regarding :

- age
- Duration of menopause.
- Duration of bleeding.
- Amount of bleeding.
- Pain associated with bleeding.
- History of diabetes.
- History of hypertension
- History of hormonal therapy
- History of discharge per vagina.

OBSTETRIC HISTORY

Detailed obstetric history was also taken in each patients regarding :

- Gravida
- Parity
- Abortion
- Last child birth.

MENSTRUAL HISTORY

a. Last menstrual period.

b. Duration of flow

c. Length of cycle

d. Amount of flow.

e. Pain during menstruation

f. Intermenstrual bleeding.

PAST HISTORY

a. Diabetes

b. Hypertension.

c. Tuberculosis.

d. Other chronic illnesses.

TREATMENT HISTORY

Patients were also asked about the treatment taken in the form of hormonal treatment to control the bleeding or other postmenopausal symptoms.

GENERAL EXAMINATION

This included :

- Built of patient
- Weight of patient
- Pulse, blood pressure and lymphadenopathy.
- Pallor
- Oedema

SYSTEMIC EXAMINATION

A thorough systemic examination was done to exclude any systemic disease.

Perspeculum Examination

These examinations were also done to exclude cervical and vagina - causes of postmenopausal bleeding.

Pervaginum examination

It was done for size, shape, duration, mobility, consistency and condition of adnexa.

INVESTIGATIONS

Investigations included - urine and blood examination with special reference to blood sugar.

Instruments used

1. Sponge holding forceps.
2. Catheter
3. Sims speculum.
4. Ant. vaginal wall retractor.
5. Vul-sellum.
6. Uterine sound.
7. Endometrial biopsy curette

Preservative

Absolute alcohol or 40% formaline solution.

Stain

1. Haematoxylin. 2. Eosin.

METHODS

It was an outdoor procedure. Patient was put in lithotomy position, valve was painted by sponge holding forceps. Bladder was evacuated in those cases where it was not evacuated already. Binnual pelvic examination was done to ascertained the position of the uterus adenexa. Sims speculum was inserted and cervix was visualised with the help of a vaginal wall retractor. One anterior lip of cervix was hold by vulsellum. Uterine sound was passed to know the exact length of the uterine cavity. Endometrial biopsy was taken by means of endometrial biopsy curettage and tissue obtained was preserved in absolute alcohol and 40% formaline. Antiseptic solution was applied on the cervix. After this tablets Medroxy progesterone acetate 10 mg B.D. for 10 days was given and patients were followed for withdrawal bleeding.

Preparation of tissue for Histopathological Examination

The tissue was processed through varying concentration of alcohol, then cleared by passing through xylol. Blocks were made by embeding, it in molten paraffin, which was allowed to set. The section was then cut and fixed on slides before staining with Ehrlich's haematoxylin and Eosin stain as described by Liliquest (1953). The slides were examined first under low power finally under high power then histological findings and clinical findings were correlated.

O B S E R V A T I O N S

OBSERVATIONS

The present study was done in the departments of Obstetrics & Gynaecology and Pathology, M.L.N. Medical College, Jhansi.

A total of 100 consecutive postmenopausal patients were studied in two groups.

Group I : Asymptomatic group including 50 postmenopausal patients without any bleeding.

Group II : Symptomatic group consisted of 50 postmenopausal patients with bleeding per vagina.

TABLE I : Distribution of cases according to age.

Age group (years)	Asymptomatic		Symptomatic	
	No.	%	No.	%
45 - 50	20	40	13	26
51 - 55	22	44	24	48
56 - 60	5	10	8	16
61 - 65	3	6	5	10
TOTAL	50	100	50	100
Mean	52.5		54.5	

Table I shows that in asymptomatic group, the maximum 22 (44%) patients were in 51-55 years of age group. Similarly in symptomatic group there were 24 (48%) patients in 51-55 years age group. Minimum 3 (6%) cases in asymptomatic group were in 61-66 years and in symptomatic group 5 (10%) patients were in 61-65 years age group.

Thus, a similar type of age pattern was seen in

TABLE II : Showing progesterone challenge test in both the groups.

Response to PCT	Asymptomatic No.	%	Symptomatic No.	%
Positive	10	20	42	84
Negative	40	80	8	16
	Z 3.3	p $<$0.05	Z [illegible]	p $<$0.05

Table II shows that progesterone challenge test was negative in 40(80%) and in 8 (16%) patients in asymptomatic and symptomatic groups respectively and it was positive in 10(20%) and 42(84%) patients in asymptomatic and symptomatic groups respectively.

TABLE III : Showing the results of histopathological examination in relation to PCT in asymptomatic group.

Histopathological examination	Negative PCT No.	%	Positive PCT No.	%
Normal				
- Proliferative phase	18	36	1	2
- Proliferative phase with with cystic dilatation	8	16	1	2
- Atrophic endometrium	4	8	1	2
- Secretory	5	10	1	2
- Other types	5	10	-	-
Abnormal				
- Endometrial hyperplasia	-	-	4	8
- Stromal cell hyperplasia	-	-	2	4
- Adenocarcinoma	-	-	-	-
TOTAL	40	80	10	20

Table III shows that in all PCT negative

asymptomatic patients, histopathological examination was normal, however, out of 10 PCT positive patients 6(12%) patients showed abnormal histopathological examination, in which 4(8%) patients had endometrial hyperplasia and 2(4%) had stromal cell hyperplasia. 2(4%) patients had chronic endometritis, 1(2%) had tubercular endometrium and 2(4%) had scanty curattage in other type. In PCT negative cases 18(36%) had proliferative and 8(16%) had proliferative phase with cystic dilatation and 14(28%) had atrophic endometrium.

TABLE IV : Showing the results of histopathological examination in relation to PCT in symptomatic group.

Histopathological examination	Negative PCT No.	%	Positive PCT No.	%
Normal				
- Proliferative phase	1	2	5	10
- Proliferative phase with cystic dilatation	1	2	2	4
- Atrophic	1	2	4	8
- Endometritis	3	6	-	-
Abnormal				
- Endometrial hyperplasia	1	2	25	50
- Stromal cell hyperplasia	1	2	6	12
TOTAL	8	16	42	84

Table IV shows that the in PCT+ positive symptomatic patients, 31(62%) cases had premalignant lesion, 25(50%) had endometrial hyperplasia, 6(12%) had stromal cell hyperplasia, 5(10%) had proliferative phase, 2(4%) had proliferative phase with cystic dilatation and 4(8%) had atrophic endometritis.

In PCT negative symptomatic patients, 1(2%) had endometrial hyperplasia and other one (2%) had stromal cell hyperplasia, 1(2%) had proliferative phase and 1(2%) had proliferative phase with cystic dilatation. Atrophic endometrium was present in 1(2%) and 3(6%) had endometritis.

TABLE V : Showing the histopathological report in both groups according to age.

Age groups (years)	Asymptomatic group			Symptomatic group		
	Normal	Premalignant	Malignant	Normal	Premalignant	Malignant
45 - 50	20	-	-	11	2	-
51 - 55	17	5	-	4	20	-
56 - 60	4	1	-	-	8	-
61 - 65	3	-	-	2	3	-
TOTAL	44	6	-	17	33	-

Table V depicts that in asymptomatic group, 20 patients belonged to 45-50 years age group had normal histopathology followed by 17 patients in the age group of 51-55 years, while 5 patients of this age group had premalignant histology of endometrium and one patient of 56-60 years age had premalignant histology of endometrium.

In symptomatic group, 11 patients belonged to 45-50 years age group had normal histology and 2 patients of 61-65 years age group had normal histology. Maximum number (20) with premalignant histology of endometrium belonged to 51-55 years age group followed by 8 patients in 56-60 years age group. Only 2 patients of 45-50 years age group had premalignant histology of endometrium.

of asymptomatic and 3 patients of symptomatic group had premalignant histology of endometrium.

TABLE VIII : Showing the blood pressure in different groups.

Diastolic B.P.(mm Hg)	Asymptomatic group No.	%	Symptomatic group No.	%
⟨ 80	46	92	35	70
80 - 90	2	4	10	20
⟩ 90	2	4	5	10
TOTAL	50	100	50	100

Table VIII shows that most of the patients, 46(92%) in asymptomatic and 35(70%) in symptomatic group were normotensives. 2(4%) patients ofasymptomatic and 10(20%) patients of symptomatic group have blood pressure in the range of 80-90 mm Hg and 2(4%) patients of asymptomatic and 5(10%) of symptomatic group were having B.P. ⟩90 mm Hg.

TABLE IX : Showing the relation of blood pressure with histopathological findings in both groups.

Diastolic B.P.(mm Hg)	Asymptomatic group			Symptomatic group		
	Normal	Premalignant	Malignant	Normal	Premalignant	Malignant
⟨ 80	40	6	-	15	20	-
80 - 90	2	-	-	1	9	-
⟩ 90	2	-	-	1	4	-
TOTAL	44	6	-	17	33	-

Table IX shows that 40 patients of asymptomatic and 15 patients of symptomatic group were the B.P. was normal

had normal histology of endometrium. Six cases of asymptomatic and 20 cases of symptomatic group had premalignant histology of endometrium.

Two patients of asymptomatic and 1 case of symptomatic group where B.P. was in the range of 80-90 mm Hg, had normal histology and nine patients of symptomatic group had premalignant histology.

Two patients of asymptomatic group and 1 of symptomatic group who had 790 mm Hg B.P., had normal histology and 4 patients of symptomatic group had premalignant histology.

TABLE X : Showing blood sugar levels in patients of both the groups.

Postprandial blood sugar (mg%)	Asymptomatic group		Symptomatic group	
	No.	%	No.	%
80 - 120	43	86	27	54
121 - 140	4	8	15	30
7 140	3	6	8	16
TOTAL	50	100	50	100

Table X shows that 43(86%) patients of asymptomatic and 27(54%) patients ot symptomatic group had blood sugar levels between 80-120 mg%. Three patients of asymptomatic and 8(16%) cases of symptomatic group had blood sugar more than 140 mg%. Four cases of asymptomatic and 15(30%) cases of symptomatic group had blood sugar levels in the range of 121-140 mg%.

TABLE XI : Showing the relation of postprandial blood sugar with histopathological findings of both the groups.

Postprandial blood sugar (mg%)	Asymptomatic group			Symptomatic group		
	Normal	Premalignant	Malignant	Normal	Premalignant	Malignant
80 - 120	40	3	-	14	13	-
121 - 140	2	2	-	3	12	-
7 140	2	1	-	-	8	-
TOTAL	44	6	-	17	33	-

Table XI shows that 40 cases of asymptomatic group had normal blood sugar levels (80-120 mg%) had normal histology of endometrium and 16 cases of symptomatic group having blood sugar in the range of 80-120 mg% had normal histology findings.

Three cases of asymptomatic and 18 cases of symptomatic group having their blood sugar level in the range of 121-140 mg% had premalignant histology of endometrium.

Two patients of asymptomatic group having blood sugar level in the range of 80-120 mg% had premalignant histology of endometrium. 12 patients of symptomatic group having blood sugar level in the range of 121-140 mg% had premalignant histology of endometrium. One and 8 patients of asymptomatic and symptomatic group respectively having blood sugar level 7140 mg% had premalignant histology of endometrium.

TABLE XII : Showing the size of uterus in cases of both the groups.

Size of uterus	Asymptomatic group		Symptomatic group	
	No.	%	No.	%
Atrophied (Smaller than normal)	20	40	2	4
Normal	22	44	26	52
6-8 weeks	6	12	20	40
7 8 weeks	2	4	2	4
TOTAL	50	100	50	100

Table XII shows that in asymptomatic group, 22(44%) patients had normal size uterus, 6(12%) cases had 6-8 weeks sized uterus and only 2 patients had their uterus 7 8 weeks in size. 20(40%) cases had their uterus size smaller than normal.

In symptomatic group, 26(52%) cases had normal uterus in size, 20(40%) cases had 6-8 weeks size and 2(4%) cases had their uterus size more than 8 weeks.

TABLE XIII : Relation of size of uterus with histological findings in both groups.

Size of uterus	Asymptomatic group			Symptomatic group		
	Normal	Prema-lignant	Malig-nant	Normal	Prema-lignant	Malig-nant
Atrophied	20	-	-	2	-	-
Normal size	20	2	-	10	16	-
6-8 weeks	2	4	-	5	15	-
7 8 weeks	2	-	-	-	2	-
TOTAL	44	6	-	17	33	-

Table XIII shows that in asymptomatic group, 20 patients with atrophied uterus had normal histology of endometrium and 20 patients having normal size uterus had normal histology of endometrium. Two cases with 6-8 and 7/8 weeks uterus had normal histology of endometrium. Four cases with 6-8 weeks uterus had premalignant histology of endometrium. There was no malignant case in this group.

In symptomatic group, 16 cases with normal size uterus and 15 with 6-8 weeks uterus had premalignant histology of endometrium. Two cases with 7/8 weeks size uterus had premalignant histology of endometrium. 10 cases with normal size uterus had normal histology of endometrium.

TABLE XIV : Distribution of cases according to duration of menopause.

Duration of menopause(yrs)	Asymptomatic group		Symptomatic group	
	No.	%	No.	%
1.5 - 5	22	44	35	70
6 - 10	20	40	12	24
11 - 15	6	12	2	4
16 - 20	2	4	1	2
TOTAL	50	100	50	100

Table XIV shows that maximum number (22) of patients in asymptomatic and 35 in symptomatic group had menopause /5 years duration. Twenty cases of asymptomatic and 12 cases of symptomatic group had menopause 6-10 years. Only 2 cases ofasymptomatic and 1 case of symptomatic had menopause more than 16 years but /20 years.

TABLE XV : Showing relation of duration of menopause with histological findings in both groups.

Duration of menopause (years)	Asymptomatic group			Symptomatic group		
	Normal	Prema-lignant	Malig-nant	Normal	Prema-lignant	Malig-nant
½ - 5	20	2	-	10	25	-
6 - 10	18	2	-	6	6	-
11 - 15	5	1	-	1	1	-
16 - 20	1	1	-	-	-	-
TOTAL	44	6	-	17	33	-

Table XV shows that in asymptomatic group 20 cases of asymptomatic having ½-5 years menopause had normal histology of endometrium and 2 patients with ½-5 years menopause had premalignant histology of endometrium. 18 and 2 cases with 6-10 years menopause had normal and premalignant histology respectively. One case with 16-20 years menopause had normal and premalignant histology each.

In symptomatic group, 10 and 6 cases with ½-5 and 6-10 years menopause respectively had normal histology of endometrium. Maximum 25 patients with ½-5 years menopause had premalignant histology of endometrium. One patient had premalignant histology of endometrium in 11-15 yrs. menopause.

Table XVI shows that maximum number (24) of cases in asymptomatic group had more than para 4 followed by 9 (18%) cases in 4th para.

Fifteen (30%) patients of symptomatic group had 3rd para and 4th para each. Only 1(2%) case in symptomatic group was nulli parous.

TABLE XVI : Distribution of cases according to parity.

Parity	Asymptomatic group No.	%	Symptomatic group No.	%
Nulli parous	3	6	1	2
Primiparous	3	6	2	4
2nd para	3	6	7	14
3rd para	8	16	15	30
4th para	9	18	10	20
74th para	24	48	15	30
Mean	4.5		3.5	

Mean parity was 4.5 in asymptomatic group and 3.5 in symptomatic group (Table XVI).

TABLE XVII : Showing the age of menopause in case of both the groups.

Age group (years)	Asymptomatic group No.	%	Symptomatic group No.	%
∠ 40	1	2	-	-
41 - 45	22	44	6	12
46 - 50	22	44	14	28
51 - 55	5	10	30	60
TOTAL	50	100	50	100
MEAN	44.2		47	

Table XVII shows that in asymptomatic group, maximum number (22) of cases had menopause in the age group of 41-45 and 46-50 years each.

In symptomatic group maximum number (30) of cases had menopause in the age group of 51-55 years followed by 14 (28%) cases in the age group of 46-50 years.

One (2%) patient in asymptomatic group had menopause in ⟨40 years of age.

TABLE XVIII : Showing the correlation of age and histopathological findings with PCT.

Histological findings	Negative PCT Age (years)		Positive PCT Age (years)		Total
	⟨ 50	⟩ 50	⟨ 50	⟩ 50	
Asymptomatic group					
Normal	20	20	-	4	44
Abnormal	-	-	-	6	6
Symptomatic group					
Normal	6	-	7	4	17
Abnormal	2	-	-	31	33

Table XVIII shows that in asymptomatic group, abnormal endometrium was present in 6 patients with ⟩50 years of age in positive PCT where 31 patients in symptomatic group shows abnormal histological findings in the same age group. The difference was significant.

Table XIX shows that in asymptomatic group, PCT positive result had no correlation with duration of menopause. But in symptomatic group it was seen that patients who had positive PCT had abnormal endometrium. 24(48%) patients in symptomatic group were having menopause less than 5 years duration.

TABLE XIX : Showing the correlation among duration of menopause, endometrial findings and PCT.

Type of endometrium	Positive PCT Duration (years) ½-5	Positive PCT Duration (years) 7 5	Negative PCT Duration (years) ½-5	Negative PCT Duration (years) 7 5
Asymptomatic group				
Normal	18	20	2	4
Abnormal	-	2	2	2
Symptomatic group				
Normal	4	3	6	4
Abnormal	1	-	24	8

TABLE XX : Showing the correlation among age of menopause, histological findings and PCT.

Type of endometrium	Negative PCT Age (years) ∠ 50	Negative PCT Age (years) 7 50	Positive PCT Age (years) ∠ 50	Positive PCT Age (years) 7 50
Asymptomatic group				
Normal	40	-	3	1
Abnormal	-	-	2	4
Symptomatic group				
Normal	8	-	2	7
Abnormal	-	-	5	28

Table XX shows that there was no correlation between PCT positive results and age of menopause in asymptomatic group whereas it was seen that about equal number of cases having positive PCT had menopause at the age of ∠50 and 750 years of age.

In symptomatic group, with abnormal endometrium and age of menopause at ⩾50 years, 28 patients had positive PCT whereas, 5 patients were of ⩽50 years of age with abnormal endometrial in symptomatic group.

Table XXI shows that in asymptomatic PCT negative group, maximum number (35) cases in range of 40-50 kg weight had normal histology and only 5 asymptomatic PCT negative cases were in 40-50 kg weight range. Four asymptomatic PCT negative patients were in the range of 51-70 kg and 6 cases of PCT positive having abnormal histology were in the 51-70 kg weight range.

In symptomatic group having weight in the range of 40-50 kg only 8 cases had normal histology and 9 symptomatic PCT positive cases had normal histology and 5 symptomatic PCT positive had weight in the range of 40-50 kg and 28 symptomatic PCT positive cases had abnormal histology.

So it was concluded that there was a definite correlation among symptomatology, increase of weight and PCT positivity.

Twenty one symptomatic PCT positive cases having blood sugar ⩾121 mg% had abnormal histology and only 6 asymptomatic PCT positive cases having abnormal histology were having ⩾121 mg% blood sugar.

So it can be said that there was a relation among high blood sugar, symptomatology and PCT positivity.

TABLE XXI : Showing correlation among weight, blood sugar, blood pressure and PCT results.

Type of endometrium	NEGATIVE PCT						POSITIVE PCT					
	Weight (kg)		Blood sugar (mg%)		B.P. (mm Hg)		Weight (kg)		Blood sugar (mg%)		B.P. (mm Hg)	
	40-50	51-70	<120	>121	<90	>90	40-50	51-70	<120	>121	<90	>90
Asymptomatic group												
Normal	35	5	40	3	40	-	-	4	3	1	4	-
Abnormal	-	-	-	-	-	-	-	6	-	6	4	2
Symptomatic group												
Normal	8	-	-	8	4	-	9	-	7	2	13	-
Abnormal	-	-	-	-	4	-	5	28	12	21	24	5

It is also seen in table XXI that 4 symptomatic PCT negative cases had abnormal histology whose diastolic blood pressure was ⟨90 mm Hg and 24 symptomatic PCT positive patients had abnormal histology whose diastolic blood pressure was ⟨90 mm Hg and 5 symptomatic PCT positive patients had abnormal histology whose diastolic blood pressure was ⟩90 mm Hg and no patient was present in PCT negative group whose diastolic blood pressure was ⟩ 90 mm Hg.

D I S C U S S I O N

DISCUSSION

In symptomatic PCT positive cases, 31 had premalignant histology. Endometrial hyperplasia (25) and cell hyperplasia (6), Flase positive were 26%. In PCT negative group, false negative was 25%. These 25% of cases could be missed by PCT. If we take out of 50 cases the false negative would be only 4% and again false positive would be 22%. This shows that 96% of whole population could be screened with PCT and 4% would be left. In consideration with the cost of investigation, PCT would be an ideal investigation for screening main whole population for endometrial carcinoma as it detects 96% of cases. False positive of 22% is a bit high but these cases could go for endometrial biopsy.

In asymptomatic PCT negative cases, no patient had premalignant histology showing that in them. PCT negativity was 100% of their having normal endometrium. False positive was seen in 4 cases giving 40%. But we take out of 50 cases then false positive would be 8% which is small and these cases go for endometrial biopsy. Incidence of endometrial and stromal cell hyperplasia in our study in symptomatic group was 64% and in asymptomatic group it was 12%.

If both the groups were combined, the incidence was 39%. Sutherland (1961) reported an incidence of 39.4%. Solopurkar (1983) reported an incidence of 42.85% of endometrial hyperplasia. In symptomatic group the incidence according to the present study being 64%, is a bit high.

In the present study, the patients were in the age group of 45 to 65 years. The mean age in asymptomatic group was 52.5 years while in symptomatic group it was 54.5 years. In asymptomatic group the maximum number of cases were in the age group of 51-55 years i.e. 22(44%) cases. In symptomatic group also maximum number of cases were in the age group of 51-55 years, was followed by 20(40%) cases in asymptomatic and 13(26%) cases in symptomatic group in the age group of 45-50 years. There was no case below the age of 40 years in both the groups. Similar type of age pattern was observed by Marks and Isacies (1981) and Koss et al (1981). Maximum number of patients were found in the age group of 50-59 years. So this period seems to be susceptible to develop endometrial premalignancy or malignancy.

In asymptomatic group, maximum number of cases having premalignant histology (5 cases) belonged to the age group of 51-55 years. In symptomatic group, 20 cases had premalignant histology and 4 cases had normal histology in the age group of 51-55 years.

TABLE XXII : Showing the incidence of endometrial hyperplasia and adenocarcinoma with age in different series.

Name of author	Premalignant	Malignant
Sippe, 1962	46.55	60-70
Cambrell	-	7 55
Koss et al, 1981	45-55	60-70
Present study, 1998	51-55	-

In the present study, in asymptomatic group 35 cases had their weight in the range of 40-50 kgs and 10 cases in the range of 51-60 kg and 5 cases in the range of 61-70 kg. In symptomatic group, 22 cases had their weight in the range of 51-60 kg and 6 cases in the range of 61-70 kg. Very few cases had their weight more than 61 kg. This might be because of the fact that obesity is rare to be found in this belt of country. But it could be seen that 30@ of cases had their weight more than 51 kg in asymptomatic group whereas in symptomatic group it was 56%. Koss et al (1981) have shown that overweight is associated with some abnormality of genital tract.

Way (1947), Peterson (1960), Gusberg (1976) and Gambrell (1980) showed that increased weight is an important risk factor for endometrial carcinoma. Gambrell (1976) stated that the risk for endometrial carcinoma in large and obese women has been known for many years.

In asymptomatic group in the present study 6(12%) cases had premalignant histology of endometrium having their weight more than 51 kg whereas in symptomatic group 21(42%) cases had premalignant histology of endometrium who had their weight more than 51 kg. Mc Donald and co-workers (1974) studied 38 postmenopausal patients varying in body weight from 29 to 430 pounds and found a direct and highly significant correlation in the metabolic rate of conversion of androstemedione to estrome with increasing weight. Gusberg and Hale (1961) showed that cancer of the body of the uterus has definite relationship with obesity.

In the present study, 2(4%) cases of asymptomatic group had diastolic blood pressure (DBP) more than 90 mm Hg and 5 symptomatic (10%) cases had DBP more than 90 mm Hg. Hanna et al (1983) reported 30% patients with hypertension. In the present study there were 14% hypertensive patients.

In asymptomatic group none of the patient having more than 90 mm Hg DBP had premalignant histology of endometrium whereas in symptomatic group 4 patients had premalignant histology who had their DBP more than 90 mm Hg. Gusberg and Hall et al (1961) showed that there is definite relation ship between cancer of the body of uterus and hypertension.

In asymptomatic group 4(8%) cases had their blood sugar between 121-140 mg% and 3(6%) cases more than 141 mg% and in symptomatic group 15(30%) cases had blood sugar between 121-140 mg% and 8(16%) cases had more than 141 mg%.

In asymptomatic group, 3(6%) cases had premalignant histology who had blood sugar more than 120 mg% whereas in symptomatic group, 23(46%) cases had premalignant histology who had blood sugar more than 120 mg%. Way (1942), Kaplan (1974) and Smith (1975) reported an association between high blood sugar level and development of endometrial hyperplasia. 20 cases in asymptomatic group had atrophic uterus and 22 cases had normal sized uterus, 8 cases had their uterine size 6 weeks. In symptomatic group 46(92%) had their uterine size between normal and 8 weeks whereas in asymptomatic group 28(56%) cases had their uterine size between normal and 8 wks. 20(40%) cases had atrophic uterine size in asymptomatic group whereas only 2 (4%) cases had atrophic uterine size.

This difference was because of presence of oestrogen in symptomatic group whereas in asymptomatic there was withdrawal of oestrogen which causes atrophy of uterus. In asymptomatic group 2 cases with normal sized uterus had premalignant histology whereas in symptomatic group 16 cases with normal sized uterus had premalignant histology. 4 cases in asymptomatic group with 6-8 weeks sized uterus had premalignant histology whereas in symptomatic group 5 cases had premalignant histology. 2 cases with uterine size more than 8 weeks had premalignant histology whereas in asymptomatic group with uterine size more than 8 weeks none had premalignant histology.

Jeffcoat (1982) found an incidence of 30% of adenocarcinoma in patients having fibroid uterus.

In asymptomatic group, 22 cases had menopause between ½ to 5 years and 20 cases had between 6-10 years. Six cases between 11-15 years and only 2 cases between 16-20 years, whereas in symptomatic group 35 cases had menopause ½ to 5 years and 12 cases had between 6-10 years, 2 cases had between 11-15 years and only one case had menopause between 16-20 years.

In present study, it was observed that 35(70%) cases in symptomatic group as compared to 22(44%) cases in asymptomatic group had their menopause between ½-5 years. More patients in former group presented with bleeding per vagina. This was because of excessive production of oestrogen from adrenal cortex, ovary or peripheral conversion of androstenedione which leads to hyperplasia and sloughing of hyperplastic endometrium.

In the present study, there were 3(6%) multiparous cases in asymptomatic group as compared to 1 case in symptomatic group. 24(48%) cases were grandmultipara inasymptomatic group whereas 15(30%) cases in symptomatic group.

In asymptomatic group 26(52%) cases were ⩽4 parity whereas in symptomatic group had lesser children as compared to asymptomatic group. Mean parity was 3.5 in symptomatic group and 4.5 was in asymptomatic group.

In the present study, 45 asymptomatic cases had attained their menopause by the age of ⩽50 years whereas in symptomatic group only 11 cases had attained their menopause by this age.

Five(10%) cases in asymptomatic group had attained menopause between 51-55 year whereas in symptomatic group there were 30(60%) cases. More cases in symptomatic group had late onset of menopause so these women had longer reproduction period as they were exposed to oestrogen for longer period as compared to asymptomatic group.

In asymptomatic group, 6(12%) cases had premalignant histology who attained their menopause at the age of ⩾45 years whereas 30(60%) cases had premalignant histology who attained menopause at ⩾45 years in symptomatic group.

Findings of present study are in agreement with many workers (Way, 1967, Gusberg, 1976, Koss et al, 1981 and Hanne et al, 1983, Jeffcoat, 1983). The risk of endometrial carcinoma was 2-4 fold in those patients who had late menopause (Gusberg, 1976).

TABLE XXIII : Showing the age of menopause in different series in relation to histological findings.

Name of authors	Age in years	
	Malignant	Premalignant
Way, 1947	46.5	57.5
Ousberg, 1981	45.5	52.5
Gambrell, 1981	46.5	57.5
Kaur et al, 1981	45.49	50.5
Hanno et al, 1983	52.0	52.0
Present study, 1998	-	47.0

An attempt was also made to find out any correlationship between PCT positivity and different variables in both the groups (asymptomatic and symptomatic). It was found that in asymptomatic group there was 6:1 ratio of chance to have abnormal endometrium in patients of more than 50 years and below the 50 years of age and that was 31:1 ratio in symptomatic group.

It was also found that in symptomatic group 8 PCT positive patients had premalignant histology where the duration of menopause was more than 5 years while in asymptomatic group only 2 patients with PCT positive had premalignant histology. Therefore, it is clear that PCT positive symptomatic patients with duration of menopause more than 5 years had greater chance to develop premalignant histology.

Similarly it was seen that 28 symptomatic PCT positive patients had premalignant histology while no patient in PCT negative group. So it is clear that overweight PCT positive and symptomatology had greater chance to develop premalignant lesion of endometrium.

In the symptomatic group with PCT positive patients with DBP 790 mm Hg, 5 cases had premalignant lesion whereas none of the patient with PCT negative had premalignant histology. So it is clear that hypertension is another risk factor in PCT positive symptomatic patients to develop premalignant histology of endometrium.

It was seen that in symptomatic group with PCT positive 21 patients had premalignant lesion of endometrium where blood sugar level was more than 121 mg%, while there was no patient in PCT negative group.

In asymptomatic group with PCT positive, 6 cases had premalignant histology of endometrium where blood sugar level was more than 121 mg% as compared to no patient in PCT negative group. Therefore, there was a definite correlationship between high blood sugar levels, PCT positivity and development of premalignant lesion of endometrium in asymptomatic group also.

Seven patients in symptomatic group with more than 50 kg weight had false positive (28%) but out of total 50 cases it would be 14%.

In symptomatic group, 4 patients with DBP 790 mm Hg, had premalignant histology showed 20% false PCT positivity. But out of total 50 cases, it would be 2%. Then 2% cases went for biopsy.

If the results are interpretted in terms of these factors, an idea of about the condition for endometrium can be gathered even in those patients who others would later on show PCT results to either false positive or

false negative. Once blood sugar of these patients is high one would be cautioned about endometrium and endometrial biopsy is must in these patients.

Thus, from the above, it was concluded that by this simple PCT, the patients could be screened in out patient department who are likely to have malignancy or endometrium particularly in those who have already other risk factors viz. hypertension, obesity and diabetes.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

The present study was conducted in the departments of Obstetrics & Gynaecology and Pathology, M.L.B. Medical College, Hospital, Jhansi.

One hundred patients were taken for the study. Each patient was examined clinically and detailed history was taken. They were subjected to progesterone challenge test (PCT) and were divided into two groups.

Group I : Fifty postmenopausal patients without any bleeding per vagina.

Group II : Fifty postmenopausal patients with bleeding per vagina.

In asymptomatic group, 30 patients were of $\bar{7}$51 years of age and in symptomatic group, 37 patients were in this age group. Ten and 42 cases of asymptomatic and symptomatic groups respectively were positive for PCT. 40 cases of asymptomatic and 8 cases of symptomatic group were negative for PCT. Forty cases of asymptomatic group with negative PCT had normal histology of endometrium and 6 cases with positive PCT had premalignant lesion of endometrium.

In symptomatic group, 31 cases with positive PCT had premalignant lesion and 2 cases with negative PCT were having premalignant lesion. Majority of the cases of both the groups were of $\angle$50 years of age. Five patients in asymptomatic group between 51-55 years of age had premalignant lesion whereas 20 patients in symptomatic group between

51-55 years age group had premalignant lesion.

Fifteen asymptomatic cases had their weight ⩾50 kg whereas 28 symptomatic cases were in this weight group. Six cases of asymptomatic and 22 cases of symptomatic group of this weight group had premalignant lesion.

Two cases of asymptomatic and 5 cases of symptomatic group had diastolic blood pressure (DBP) ⩾90 mm Hg. Among these asymptomatic cases no patient had premalignant histology whereas 4 cases of symptomatic group had premalignant lesion.

Maximum patients in present study had their blood sugar levels <120 mg%, there were 86% in asymptomatic and 56% in symptomatic group having <120 mg% blood sugar. 20(40%) cases of symptomatic having ⩾120 mg% blood sugar had premalignant lesion whereas 3(6%) cases had premalignant lesion in asymptomatic group.

Maximum number (84% in asymptomatic and 56% in symptomatic group) of patients had their uterine size ≤ normal size. Two patients each in asymptomatic and symptomatic group had their uterine size more than 8 weeks. Six cases of asymptomatic group with ⩾ normal size uterus had premalignant lesion of endometrium and in symptomatic group 33 patients with ⩾ normal size uterus had premalignant histology.

Maximum number (22 cases in asymptomatic and 35 cases in symptomatic group) had their menopause <5 years of duration. Only 2 cases of asymptomatic and 1 case of symptomatic group had their duration of menopause ⩾15 years.

Twenty five cases of symptomatic group with ⩽5 years duration of menopause had premalignant histology whereas only 2 cases of asymptomatic group with ⩽5 years duration of menopause had premalignant histology. There were higher number of symptomatic cases with PCT positive in the present study than asymptomatic group.

Twenty four cases in asymptomatic group were of grandmultipara and 15 cases of symptomatic group. The cases of symptomatic group were of lesser parity in comparison to asymptomatic group.

Twenty three (46%) cases of asymptomatic group attained menopause at ⩽45 years of age and only 6(12%) cases of symptomatic group attained menopause at this age. Thirty patients in symptomatic and 5 in asymptomatic group attained menopause after 50 years of age. Out of these, 3 cases in asymptomatic and 20 cases of symptomatic group had premalignant histology of endometrium.

Twenty eight PCT positive symptomatic cases with ⩾50 kg weight had premalignant lesion whereas only 6 patients with positive PCT with ⩾50 kg weight of asymptomatic group had premalignant lesion and no patient of asymptomatic PCT negative with ⩾50 kg weight had premalignant lesion. Twenty one PCT positive symptomatic cases had premalignant lesion as compared with no patient in asymptomatic PCT negative patients whose blood sugar level was ⩾121 mg%.

Five PCT positive symptomatic patients had premalignant lesion of endometrium as compared to zero patients in

asymptomatic PCT negative group whose diastolic blood pressure was more than 90 mm Hg.

Conclusion

The following conclusions were drawn from the present study :

1. Late menopause, overweight, diabetes, decreased parity and hypertension are the important risk factors associated with carcinoma body uterus.
2. Postmenopausal women both symptomatic and asymptomatic could be screened for developing premalignant lesion of endometrium by PCT.
3. Premalignant lesions are most common in 5th decade of life.
4. PCT positive asymptomatic women are also at risk of developing malignancy and have other associated risk factors viz. obesity, hypertension, decreased parity and diabetes.
5. Thirty one symptomatic PCT positive cases had premalignant histology. False negative PCT is 4%. This shows that by PCT in symptomatic 96% of the population could be diagnosed to detect premalignant lesion of endometrium.
6. In asymptomatic PCT negative cases, no patient had premalignant histology. It means, there is no possibility to have premalignant lesion in these patients. False PCT positive in asymptomatic group was 8%.

7. Incidence of endometrial hyperplasia was 64% in symptomatic group and 12% in asymptomatic group in this study.

8. Four (8%) cases in asymptomatic group had false positive PCT. They were having ⩽51 kg weight and had normal histology. However it is important that endometrial biopsy should be performed in each PCT positive patient.

9. Asymptomatic patients with increased weight, diabetes, decreased parity and hypertension may have increased risk of developing premalignant histology of endometrium.

10. Twenty symptomatic patients had blood sugar level ⩾121 mg% and 21 PCT positive symptomatic cases had abnormal histology of endometrium. So false positive was 8.6%. But all the patients of present study are considered, it would be 4%. This 4% can be called for regular follow up for the development of premalignant lesion of endometrium.

11. Five symptomatic patients had diastolic blood pressure ⩾90 mm Hg and 5 PCT positive patients had premalignant lesion in symptomatic group. So there was no false positive.

B I B L I O G R A P H Y

BIBLIOGRAPHY

1. Anderson B. et al. Routine noninvasive hysterography in the evaluation and treatment of endometrial carcinoma. Gynecol. Oncol, 1974; 4 ; 354.

2. Backer J.Z. Wal Carcinoma Corporis uteri sentan. Gynaecol, 1964.

3. Bonham D.G. and Bonham RJG. Cancer of the endometrium an improved epidemiological assessment. Aust. N.Z.J. Obstet Gynaecol, 1973; 13 : 172.

4. Chakravorty et al. Brit Med Jr, 1976; 2764.

5. Cohen CI, Gusberg SB and Koffer D. Histological screening for endometrial cancer. Obst. Gynaecol. 1974; 279-280.

6. Cohen CJ and Deppe G. Endometrial carcinoma and oral contraceptive agents. Obst Gynec, 1977; 49 : 390.

7. Creasman WL et al. Adenocarcinoma of the endometrium its metastatic lymph node potential, A preliminary report. Gynae. Oncol, 1976; 4 ; 239.

8. Creasman WT and Reed JC. Screening techniques in endometrial cancer. Cancer, 1976; 38 : 436.

9. David Anderson MD. The cytologic diagnosis of endometrial adenocarcinoma. Amer Jr June 1, 1976.

10. Dunn LJ and Bradbury JT. Endocrine factors in endometrial carcinoma. A preliminary report. Amer. Jr Obstet Gynaec, 1967; 97 : 465.

11. Dunn LJ, Merchant JA, Bradbury JT and Stone JT. Glucose tolerance and endometrial carcinoma. Arch Intern Med, 1968; 121 : 236.

12. Elwood JM et al. Cancer Institute, 1977; 59 : 1005. Quoted by Koss et al, 1980.

13. Finn WF. Time, site and treatment of recurrence of endometrial carcinoma. Arch Intern Med, 1968; 121:236.

14. Fox et al. Endometrial cytology ; a new technique. Amer J Obstet Gynae, 1962; 83 : 1562.

15. Gambrell RD. Oestrogen progesterone and endometrial carcinoma. Reprod Med, 1977; 18 : 301-306.

16. Cambrell et al. Use of progesterone challenge test to reduce risk of endometrial carcinoma. 1980; 56(6).

17. Gravlee IC. Jet irrigation method : for diagnosis of endometrial adenocarcinoma. Obst Gynec.1973; 34:168.

18. Gusberg SB. Precancer of corpus carcinoma oestrogen and adenomatous hyperplasia. Amer J Gynae, 1947.

19. Gusberg SB and Kaplan AL. Precursors of corpus cancer : Adenomatous hyperplasia as stage 0 carcinoma of the endometrium. Amer J Obstet Gynaecol, 1963; 97 : 662.

20. Gusberg SB, Chen SY and Cohen CJ. Endometrial cancer : factors influencing the choice of therapy. Gynecol Oncol, 1974; 2 : 308.

21. Gusberg SB. The individual at high risk for endometrial carcinoma. Amer J Obstet Gynaecol, 1976; 126 : 535.

22. Hanna et al. Detection of postmenopausal women at risk for endometrial carcinoma by a progesterone challenge test. Amer J Obstet Gynaecol, Dec. 15, 1983.

23. Hecht EL. Amer J Obstet Gynaecol, 1956; 71 : 917;1956.

24. Herling AT, Somers SC. Genesis of endometrial carcinoma study of prior biopsy cancer, 1949.

25. Hofmeister FJ. Endometrial biopsy. Amer J Obst Gynaec, 1974; 118 : 773.

26. Jeffcoate. Principles of Gynaecology, 1983.

27. Kaplan and Cole. Precursor of corpus cancer IV. Adenomatous hyperplasia as stage 0 carcinoma of endometrium. Amer Jr Obstet Gynaec, 1953; 67 : 62.

28. Kelly RM and Faber WM. Progestational agents in the treatment of carcinoma of the endometrium. New Engl Jr Med, 1973; 264 : 216.

29. Kelley HA. Curettage without anaesthesia on the office table. Amer J Obst & Gynaecol, 1975; 9 : 78-80.

30. Kistner RW. Endometrial hyperplasia and carcinoma in situ. In Stall B.A.(ed.), Endocrine therapy in malignant disease. Philadelphia WB Saunders, 1972.

31. Kottmeier H and Kolstad P (eds.). Annual report. Gynaecological cancer. F.I.G.O., Stockholm, 1976; 16.

32. Koss MD. Screening of asymptomatic women for endometrial cancer. Jr Amer Coll. Obstet & Gynaecol, 1981.

33. Mac Donald PC and Siiteri PK. The relationship between extraglandular production of estrone in the occurrence of endometrial hyperplasia. Gynaecol Oncol, 1974; 2:259.

34. Mac Mahon B. Gynaecol Oncol, 1974; 2 : 272.

35. Mac Donald TW. Exogenous estrogen and endometrial carcinoma in case control and incidence. Amer J Obstet Gynaecol, 1977; 127 : 572.

36. Mc Bride JM. J Obstet Gynaec Brit Emp. 1959; 61 : 691.

37. MiMarks and Isacics. Jr Amer Coll. Obstet Gynec., 1981.

38. Mc Guire TH. Efficacy of endometrial biopsy in the diagnosis of endometrial carcinoma. Obstet Gynaec, 1962; 19 : 105-107.

39. Novak E., and Bal S. Relation of endometrial hyperplasia to adenocarcinoma of the uterus. Amer J Obstet. Gynaec, 1936; 32 : 674.

40. Novak E. and Richardson GH. Amer J Obstet Gynaecol, 1941; 42 : 564.

41. Palmer et al. Comparison of aspiration curettage with conventional dilation and curettage. Amer J Obstet Gynec. 1950; 60 : 671-674.

42. Peterson EP. Endometrial carcinoma in young women : A clinical profile. Obstet Gynaecol, 1968; 31 : 702.

43. Peter CM, Young PHD. Progesterone binding in human endometrial carcinoma. Amer Jr Obstet Gynaec, April 1, 1975.

44. R. Don Gambrell. Hormones and endometrial carcinoma. Amer J Obstet Gynaec, 1978.

45. Reagon JM, Sommers SC. Genesis of endometrial carcinoma study. Amer J Obstet & Gynaec., 1954.

46. Reifenstein ECJ. The treatment of advanced endometrial cancer with hydroxyprogesterone caproate. Gynaecol Oncol, 1974; 2 : 377.

47. Schwartz PE, Kohorn et al. Routine use of hysterography in endometrial carcinoma and postmenopausal bleeding. Obstet Gynaecol, 1975; 45 : 378.

48. Sippe. Endometrial hyperplasia and uterine bleeding, 1962.

49. Siiteri et al. Estrogen receptors and the esterone hypothesis in relation to endometrial and breast cancer. Gynae, Oncol, 1974; 2 : 228.

50. Smith et al. Association of exogenous estrogen and endometrial carcinoma. New Engl Med, 1949; 293:1164.

51. Smith et al. New Engl Med, 1949; 293 : 1164.

52. Sutherland. Integrated obstetrics and gynaecology for postgraduates. London, Boston, 3rd ed. 1981,p. 580.

53. Solapurkar. Deptt of Obstet Gynaecol. Dr. V.M. [illegible], Medical College and General Hospital, Solapur. Endometrial spectra in women at different ages. J Obstet & Gynaecol of India.

54. Walter D, Robinson D, Park RC and Potow WE. Diagnostic out patients aspiration curettage. Obstet Gynaecol, 1975; 46 : 160-164.

55. Way S. The aetiology of carcinoma of the body of the uterus. J Obstet Gynaecol Brit Emp., 1947; 103 : 810.

56. Way S. The aetiology of carcinoma of the body of the uterus. J Obstet Gynaecol Brit,Emp, 1954; 61 : 46.

57. Williams TJ and Woodruff JD. Similarities in malignant mixed mesenchymal tumours of the endometrium. Obstet Gynaec Survey, 1968; 17 : 1.

58. William T, Greasman. Screening technique in endometrial carcinoma. Cancer, 1976; 38 : 436-440.

59. Wide L. et al. Acta Endocrinology (Suppl), 1973; 174.

60. Welch WR and Scully RE. Precancerous lesion of endometrium. Path. 1977.

61. Woodruff JD and Julian GC. Multiple malignancy of upper genital tract. Amer J Obstet Gynaecol, 1969.

62. Wyndes EL, Escher GC and Mantel N. The epidemiological investigation of cancer of the endometrium. Cancer, 1966; 19 : 489.
